

**IN THE CLAIMS:**

The following listing of claims replaces all prior versions and listings of claims in the application.

1. (Previously Presented) A bioreactor, comprising:

(a) a housing having an inner side comprising: a gas introduction means integral to the housing; and a gas expiration means integral to the housing;

(b) a plurality of modules of hollow fibers, residing within the housing, each module comprising:

(i) at least three coaxially arranged hollow fibers, each hollow fiber having an inner side and an outer side, including an innermost hollow fiber and an outermost hollow fiber;

(ii) at least three compartments, comprising: a first compartment defined by an inner side of an innermost hollow fiber and at least two compartments defined by a respective annular space between adjacent fibers of the at least three coaxially arranged hollow fibers; and

(c) an outermost compartment defined by a space within the inner side of the housing which is not occupied by the plurality of modules;

in which at least one compartment is charged with a gaseous nutrient substantially free of non-gaseous fluids.

2. (Original) The bioreactor of claim 1, where the hollow fibers are semipermeable.

3. (Original) The bioreactor of claim 2, where the hollow fibers comprise a material selected from the group consisting of polysulfone, polypropylene, nylon, polyester, polytetrafluoroethylene, cellulose acetate, and mixed esters of cellulose.

4. (Original) The bioreactor of claim 1, where the first compartment, the at least one additional compartment and the outermost compartment each further comprise at least one inlet port and at least one outlet port.

5. (Original) The bioreactor of claim 1, where the bioreactor further comprises at least  $10^9$  cells.

6. (Original) The bioreactor of claim 5, where the cells are liver cells.

7. (Original) The bioreactor of claim 6, where the liver cells are selected from the group

consisting of porcine liver cells and human liver cells.

8. (Original) The bioreactor of claim 4, where the housing further comprises at least one inlet manifold and at least one outlet manifold for the first compartment and at least one inlet manifold and at least one outlet manifold for each additional compartment.

9. (Original) The bioreactor of claim 8, where at least one manifold further comprises a flow distributor.

10. (Original) The bioreactor of claim 9, where at least one compartment further comprises an extracellular matrix.

11. (Original) The bioreactor of claim 1, where at least one annular space is about 0.2 millimeters to about 0.8 millimeters.

12. (Original) The bioreactor of claim 1, where the bioreactor is sterilized by a means selected from the group consisting of autoclaving, ethylene oxide and gamma radiation.

13. (Original) The bioreactor of claim 1, wherein the innermost hollow fiber has a length of about 2 centimeters to about 50 centimeters.

14. (Original) The bioreactor of claim 8, where the housing has a first end and a second end, and

where each inlet port and each exit port are at the first end of the housing.

15. (Original) The bioreactor of claim 8, further comprising:

microfibers substantially parallel to the modules of hollow fibers.

16. (Original) The bioreactor of claim 15, where the microfibers further comprise at least one aeration inlet port and at least one aeration outlet port.

17. (Original) The bioreactor of claim 1, where at least one coaxial hollow fiber is saturated with perfluorocarbon.

18. (Original) The bioreactor of claim 1, where at least one coaxial hollow fiber has a pore size less than  $1 \times 10^{-6}$  m.

19. (Original) The bioreactor of claim 1, where at least one coaxial hollow fiber has a pore size less than  $0.1 \times 10^{-6}$  m.

20. (Original) The bioreactor of claim 1, where at least one coaxial hollow fiber has a pore size less than  $0.05 \times 10^{-6}$  m.

21. (Original) The bioreactor of claim 1, where at least one compartment further comprises cells mixed with an extracellular matrix.

22. (Original) A method of supplying cell biosynthesis products to a patient in need thereof,

comprising: pumping intravenous feeding solution through a compartment of the bioreactor of claim 5; collecting the output; and intravenously feeding the output to the patient.

23. (Previously Presented) A serially-linked bioreactor, comprising a plurality of bioreactor subunits, each bioreactor subunit comprising:

(a) a housing having an inner side comprising: a gas introduction means integral to the housing; and a gas expiration means integral to the housing;

(b) a plurality of modules of hollow fibers, residing within the housing, each module comprising:

(i) at least three coaxially arranged hollow fibers, each hollow fiber having an inner side and an outer side, including an innermost hollow fiber and an outermost hollow fiber;

(ii) at least three compartments, comprising: a first compartment defined by an inner side of an innermost hollow fiber; and at least two compartments defined by a respective annular space between adjacent fibers of the at least three coaxially arranged hollow fibers; and

(c) an outermost compartment defined by a space within the inner side of the housing which is not occupied by the plurality of modules; and

(d) at least one compartment of one bioreactor subunit linked serially to at least one compartment of at least one other bioreactor subunit;  
in which at least one compartment is charged with a gaseous nutrient substantially free of non-gaseous fluids.

24. (Original) The bioreactor of claim 23, where each bioreactor subunit further comprises at least  $10^9$  cells.

25. (Original) The bioreactor of claim 24, where the cells are liver cells.

26. (Original) The bioreactor of claim 25 where the cells are selected from the group consisting of human liver cells and porcine liver cells.

27. (Original) The bioreactor of claim 24, where at least one compartment of each bioreactor subunit further comprises an extracellular matrix.

28. (Original) A method of treating a patient in need thereof comprising:

(a) introducing plasma of a patient into a bioreactor subunit of the serially linked bioreactor of claim 23,

(b) forcing at least a portion of the plasma to flow radially through a cell compartment

of the bioreactor subunit to form a biotransformed effluent;

(c) introducing the biotransformed effluent into a second bioreactor subunit of the bioreactor of claim 23;

(d) forcing at least a portion of the biotransformed effluent to flow radially through a cell compartment of the second bioreactor subunit to form supplemented plasma; and

(e) returning the supplemented plasma to the patient's circulatory system.

29. (Canceled)

30. (Withdrawn) A method of cell culture, comprising:

introducing viable cells into a compartment of the bioreactor of claim 29, and passing nutrient medium through coaxially adjacent hollow fibers.

31. (Withdrawn) A method of manufacture of a coaxial bioreactor, comprising:

(a) bonding outer semipermeable hollow fibers to a manifold,

(b) inserting middle semipermeable hollow fibers into the outer semipermeable hollow fibers,

(c) bonding the middle semipermeable hollow fibers to a second manifold,

(d) inserting the inner semipermeable hollow fibers into the middle semipermeable hollow fibers, and

(e) bonding the inner semipermeable hollow fibers to a third manifold.

32. (Withdrawn) The method of claim 31 where inserting middle semipermeable hollow fibers into the outer semipermeable hollow fibers is vacuum-assisted.

33. (Withdrawn) The method of claim 31 where inserting inner semipermeable hollow fibers into the middle semipermeable hollow fibers is vacuum assisted.

34. (Withdrawn) An apparatus for assembly of a bioreactor, comprising:

(a) a vacuum head, attached to a negative pressure source, the vacuum head comprising: a hollow housing; a mesh to retain hollow fibers, where the mesh is affixed to the housing; and a holder for a manifold;

(b) a vessel for holding polyurethane epoxy and ends of hollow fibers.

35. (Withdrawn) A device for maintaining viable eucaryotic cells, comprising:

(a) an annular compartment, having an annular space,

(b) two compartments, adjacent and coaxial to said annular space, where each adjacent compartment contains a liquid, and

(c) an integral aeration supply for the annular space.

36. (Withdrawn) The device of claim 35, in which the annular space is about 0.2 to about 0.8 mm.
37. (Withdrawn) The device of claim 35, additionally comprising a second annular compartment having a second annular space.
38. (Withdrawn) A method of treating a patient in need thereof, the device comprising:
- (a) circulating plasma from a patient into a device, comprising:
    - (i) an annular compartment, having an annular space and a complement of eukaryotic cells therein,
    - (ii) at least two compartments, adjacent and coaxial to said annular space, where each adjacent compartment contains a liquid,
    - (iii) an integral aeration supply for the annular space; and
  - (b) allowing a portion of the plasma to traverse the annular compartment.
39. (Withdrawn) The method of claim 38, in which the said traversing is facilitated by pressure.
40. (Withdrawn) The method of claim 38, where said portion of the plasma is returned to the patient's circulation system.
41. (Withdrawn) The method of claim 38, in which said device additionally comprises a second annular compartment having a second annular space and a complement of eukaryotic cells therein.
42. (Withdrawn) The method of claim 39, in which said device additionally comprises a second annular compartment having a second annular space and a complement of eukaryotic cells therein.
43. (Withdrawn) The method of claim 40, in which said device additionally comprises a second annular compartment having a second annular space and a complement of eukaryotic cells therein.
44. (Withdrawn) The method of claim 42, in which said portion of the plasma is returned to the patient's circulation system.
45. (Withdrawn) A method of selecting a radial flow rate to enhance cell viability in a bioreactor comprising semi-permeable fibers, comprising: measuring a first hydraulic pressure associated with a first semi-permeable fiber and a second hydraulic pressure associated with a second semipermeable fiber to obtain a pressure differential and adjusting the first hydraulic pressure, the second hydraulic pressure, or a combination thereof to select

one or more radial flow rates so as to improve cell viability.

46. (Withdrawn) The method of claim 45 in which the first fiber and the second fiber are coaxial.

47. (Withdrawn) The method of claim 46 in which the radial flow rate is selected based on the formula:

$$\Delta P = \frac{Q}{2\pi L} \left[ \frac{\ln\left(\frac{r_b}{r_a}\right)}{K_1} - \frac{\ln\left(\frac{r_d}{r_c}\right)}{K_2} \right]$$

where  $\Delta P$  is the pressure differential,  $Q$  is the radial flow rate,  $L$  is the length of the shorter of the first and second fiber lengths,  $r_a$  is the radial distance from the centerline of the bioreactor to the inner surface of the first fiber,  $r_b$  is the radial distance from the centerline of the bioreactor to the outer surface of the first fiber,  $r_c$  is the radial distance from the centerline of the bioreactor to the inner surface of the second fiber,  $r_d$  is the radial distance from the centerline of the bioreactor to the outer surface of the second fiber,  $K_1$  is the hydraulic permeability of the first fiber, and  $K_2$  is the hydraulic permeability of the second fiber.

48. (Withdrawn) A computer readable medium including instructions therein for calculating a radial flow rate in a bioreactor comprising semi-permeable fibers, said instructions including the steps of:

(a) receiving measurements of hydraulic permeability for each of at least two coaxial semi-permeable fibers,

(b) receiving measurements of hydraulic pressure for at least two coaxial semi-permeable fibers, and

(c) estimating said radial flow rate between said coaxial semi-permeable fibers.

49. (New) The bioreactor of claim 1 in which the gaseous nutrient includes oxygen.

50. (New) The bioreactor of claim 49 in which the gaseous nutrient further includes carbon dioxide.

51. (New) The bioreactor of claim 1 in which the gaseous nutrient includes air.

- 52. (New) The serially linked bioreactor of claim 23 in which the gaseous nutrient includes oxygen.
- 53. (New) The serially linked bioreactor of claim 52 in which the gaseous nutrient further includes carbon dioxide.
- 54. (New) The serially linked bioreactor of claim 23 in which the gaseous nutrient includes air.
- 55. (New) The method of claim 28 in which the gaseous nutrient includes oxygen.
- 56. (New) The method of claim 55 in which the gaseous nutrient further includes carbon dioxide.
- 57. (New) The method of claim 28 in which the gaseous nutrient includes air.